HIT on Dialysis – When Is It Safe to Re-Challenge?

see Hartmann et al., pp. c143–c148

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When patients first start haemodialysis and are exposed to heparins, a mild degree of thrombocytopenia may occur due to the interaction of heparin and surface-bound platelet factor 4 (PF4) resulting in platelet activation (heparin-induced thrombocytopenia type I). Less commonly an immune-mediated thrombocytopenia may develop, known as heparin-induced thrombocytopenia type II (HIT) [1]. Typically, IgG isotype antibodies develop some 5–10 days after exposure to heparin and recognise an epitope on the heparin-PF4 complex, which results in binding to the Fcγ RIIA receptors on the platelet surface and cross-linking of the receptors. This leads to platelet activation and aggregation, and with the additional release of PF4, platelet-derived micro-particles and thrombin generation.

Cross-sectional studies in haemodialysis patients have reported the prevalence of HIT to vary from 0 to 6%, although one study reported a prevalence as high as 37% [2–4]. The incidence is less well established, with one study reporting 3.9% [5]. Although HIT typically occurs with incident patients, it can occur in chronic haemodialysis patients following coronary artery bypass surgery, or central venous access catheter insertion. It has been reported to occur more frequently with bovine than porcine unfractionated heparin (UFH), and UFH more than low molecular weight heparins (LMWHs) and heparinoids [6].

Fortunately only a minority of patients who develop these antibodies suffer clinical sequelae, due to the development of a hyper-coagulable state [1], ranging from intradialytic hypertension to access thrombosis, and clotting of the extracorporeal circuit, through to major venous thromboembolism, and sudden cardiovascular collapse shortly after the administration of UFH bolus, the so-called ‘pseudo-pulmonary embolus syndrome’ [7, 8].

The treatment of HIT is to prevent further exposure to both UFH and LMWHs, including heparin locks and flushes [8]. Initially patients require systemic anticoagulation, with direct thrombin inhibitors, and/or heparinoids [6]. Once the platelet count has recovered to $>150,000 \times 10^9/l$, oral coumarin therapy can be commenced. However, for dialysis patients additional anticoagulation is often required for intermittent haemodialysis. The anticoagulants licensed and available for treating patients with HIT vary from country to country. Argatroban, which is derived from L-arginine, is an expensive reversible direct thrombin inhibitor. It is predominantly hepatically metabolised, and has to be given by infusion. The other direct thrombin inhibitor currently licensed is lepirudin, a recombinant form of hirudin. This is renally excreted and therefore has a very extended half life in end-stage renal failure. In addition, the plasma concentration does not prolong the partial thromboplastin

tin time in a linear fashion, thus increasing the risk of haemorrhage. Hirudins can be monitored by the ecarin clotting time, but this assay is not readily available. Anti-hirudin antibodies develop in a substantial number of patients treated with lepirudin, resulting in even greater biological activity [6]. The alternative is to use the heparinoids, such as danaparoid, or fondaparinux. Even with danaparoid there is a small possibility of cross-reactivity with the HIT antibodies, so that platelet counts have to be carefully monitored [9]. Danaparoid is also mainly renally excreted, and therefore has an extended half life in dialysis patients. Thus anticoagulation has to be carefully monitored, using anti-factor Xa assays. Compared to UFH and LMWHs, the currently available anticoagulants for treating patients with HIT are expensive, and the majority are renally excreted resulting in prolonged biological activity with increased risk of haemorrhage and require careful monitoring.

Thus a key issue for haemodialysis patients with HIT is when the patient can be safely re-exposed to heparins. Hartman et al. [10] report their experience of 4 patients who developed HIT shortly after starting dialysis using bolus LMWH, nadroparin. Three of the patients had had surgery prior to starting dialysis. Interestingly, this is the first report of LMWHs causing the 'pseudo-pulmonary embolus'-like collapse during dialysis. The timing and

degree of the thrombocytopenia and exposure to LMWH coupled with the clinical picture made the probability of HIT high prior to antibody testing [6]. Laboratory confirmation was made using both a functional assay of platelet agglutination and an ELISA. The currently available ELISAs have a relatively high rate of false-positive reactions, and can also detect non-pathogenic IgA and IgM antibodies. However, the reliability can be improved by performing additional correction steps for both UFH and LMWH [8]. The patients were then switched to lepirudin for dialysis and the thrombocytopenia resolved with 12 days. Follow-up showed that the antibodies disappeared between 53 and 193 days in 3 patients, but remained positive in the other patient. Re-challenge was successful once both the functional assay of platelet agglutination and an ELISA had been performed, allowing resumption of LMWH for dialysis. This report confirms earlier studies, suggesting that in the majority of these antibodies are transient [6]. However the antibodies did not disappear in all patients, and there were differences between the assays in terms of when HIT antibodies became undetectable. Thus further studies are required to determine whether it is safe to re-challenge once a functional assay is negative but the ELISA positive, and similarly whether ELISA assays alone can reliably predict when it is safe to re-challenge.

References

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